

©1995 DERWENT INFORMATION LTD

WO9517405 A1 953132



BASIC

95246119

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

BEI

C07D 491/048, 307/79, 311/58, 491/052,
A61K 31/40 // (C07D 491/052, 311:00,
209:00) (C07D 491/048, 307:00, 209:00)

A1

(11) International Publication Number: WO 95/17405

(43) International Publication Date: 29 June 1995 (29.06.95)

(21) International Application Number: PCT/EP94/04220

(22) International Filing Date: 20 December 1994 (20.12.94)

(30) Priority Data:
9326192.3 22 December 1993 (22.12.93) GB

(71) Applicant (for all designated States except US): GLAXO
GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NORTH, Peter, Charles
[GB/GB]; Glaxo Research and Development Limited, Park
Road, Ware, Hertfordshire SG12 0DP (GB). CARTER,
Malcolm, Clive [GB/GB]; Glaxo Research and Development
Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB).

(74) Agents: GALLAFENT, Allison et al.; Glaxo Holdings plc,
Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6
0NN (GB).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH,
CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP,
KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO,
NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US,
UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF,
BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG),
ARIPO patent (KE, MW, SD, SZ).

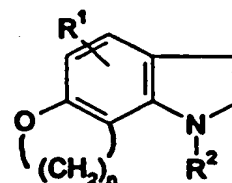
Published

With international search report.

(54) Title: INDOLINE DERIVATIVES, METHOD OF PREPARATION AND THEIR USE AS PHARMACEUTICALS

(57) Abstract

A compound of formula (I), wherein R¹ is hydrogen, halogen or C₁₋₆ alkyl;
R² is a group of formula -CR³R⁴(CH₂)_pNR⁵COR⁶; R³, R⁴ and R⁵, which
may be the same or different, are hydrogen or C₁₋₆alkyl; R⁶ is C₁₋₆alkyl or C₃₋₇
cycloalkyl; n is an integer of 2, 3 or 4; p is an integer of 1, 2, 3 or 4; and
pharmaceutically acceptable salts and solvates thereof. A compound of formula (I)
is useful in the treatment of conditions associated with a disturbed functioning of
the melatonin system.



(I)

95246119

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

WO 95/17405

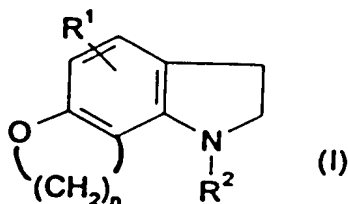
PCT/EP94/04220

1

INDOLINE DERIVATIVES, METHOD OF PREPARATION AND THEIR USE AS PHARMACEUTICALS

This invention relates to tricyclic indoline derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The invention thus provides compounds of formula (I)



wherein R^1 is hydrogen, halogen or C_{1-6} alkyl;
 R^2 is a group of formula $-CR^3R^4(CH_2)_pNR^5COR^6$;
 R^3 , R^4 and R^5 , which may be the same or different, are hydrogen or C_{1-6} alkyl;
 R^6 is C_{1-6} alkyl or C_{3-7} cycloalkyl;
 n is an integer of 2, 3 or 4;

p is an integer of 1, 2, 3 or 4;
 and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that in formula (I) hereinabove the substituent R^1 may be attached at either available position on the phenyl portion of the tricyclic ring.

As used herein, an alkyl group may be a straight chain or branched chain alkyl group. Examples of suitable alkyl groups include C_{1-4} alkyl groups, for example methyl, ethyl and isopropyl groups. A preferred alkyl group is methyl.

A halogen substituent may be, for example, fluorine, chlorine, bromine or iodine.

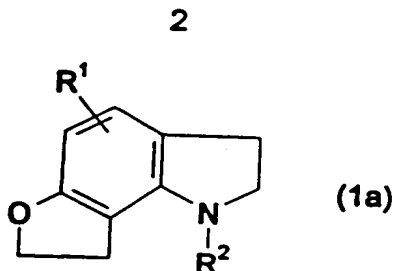
R^2 preferably represents a group $-CR^3R^4(CH_2)_pNHCOR^6$ wherein R^3 and R^4 each independently represent hydrogen or C_{1-3} alkyl (e.g. methyl), p is an integer of 1 or 2, especially 1, and R^6 is C_{1-3} alkyl (e.g. methyl) or C_{3-5} cycloalkyl (e.g. cyclopropyl or cyclobutyl).

Examples of the group R^1 include hydrogen, halogen (e.g. chlorine) and C_{1-3} alkyl (e.g. methyl).

A preferred group of compounds of the invention are compounds of formula (Ia)

WO 95/17405

PCT/EP94/04220



and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof, wherein R^1 and R^2 are as defined hereinabove.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the present invention include:

N-[2-(2,3,8,9-Tetrahydro-7H-pyrano[2,3-g]indol-1-yl)-ethyl]-acetamide;

N-[2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide;

N-[2-(5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide;

Cyclopropanecarboxylic acid [2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-amide;

and pharmaceutically acceptable salts and solvates thereof.

A particularly suitable compound according to the present invention is N-[2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide, and pharmaceutically acceptable salts and solvates thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. A particularly suitable pharmaceutically acceptable salt of the compounds of formula (I) is the hydrochloride salt. Other acids such as oxalic, while not, in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

References hereinafter to a compound of formula (I) includes the compound and its pharmaceutically acceptable salts.

The compounds of formula (I) may contain at least one asymmetric carbon atom and may exist as stereoisomers. The compounds of formula (I) thus

include the d- and l-isomers and mixtures, for example racemic mixtures, thereof.

The compounds of formula (I) are of use in the treatment of disorders which arise from a disturbed functioning of the melatonin system. In particular the compounds of formula (I) may be used in the treatment of chronobiological disorders, especially in the elderly population, glaucoma, cancer, psychiatric disorders, osteoporosis, neurodegenerative diseases or neuroendocrine disorders arising as a result of or influenced by the melatonin system.

Chronobiological disorders include seasonal affective disorders (SAD), primary and secondary insomnia disorders, primary and secondary hypersomnia disorders, sleep-wake schedule disorders (including advanced phase type, delayed phase type, disorganised type and frequently-changing type) and other dyssomnias, especially those caused by ageing, dementias, blindness shift work and by rapid time-zone travel, commonly known as jet lag.

Cancers which may be treated with a compound of formula (I) include solid tumours, e.g. melanomas and breast carcinomas.

Psychiatric disorders which may be related to altered melatonin function or influenced by melatonin and circadian rhythms include mood disorders (including bipolar disorders of all types, major depression, dysthymia and other depressive disorders), psychoactive substance dependence and abuse, anxiety disorders (including panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalised anxiety disorder), schizophrenia, epilepsy and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures), disorders of involuntary movement (including those due to Parkinson's disease, and drug-induced involuntary movements) and dementias (including primary degenerative dementia of the Alzheimer type).

Neurodegenerative diseases which may be related to altered melatonin function or influenced by melatonin and biological rhythms include multiple sclerosis and stroke.

Neuroendocrine disorders which may be related to altered melatonin function or influenced by melatonin and biological rhythms include peptic ulceration, emesis, psoriasis, benign prostatic hyperplasia, hair condition and body weight. Particular neuroendocrine disorders which may be treated include those relating to the regulation of reproductive maturation and function include

Idiopathic delayed puberty, sudden infant death, premature labour, infertility, antifertility, premenstrual syndrome (including late luteal phase dysphoric disorder) and sexual dysfunction (including sexual desire disorders, male erectile disorder, post-menopausal disorders and orgasm disorders). The compounds may also be used to manipulate breeding cycles, body weight, coat colour and oviposition of susceptible hosts, including birds, insects and mammals. The compounds of formula (I) may also have sedative, anti-inflammatory and analgesic effects, effects on the microcirculation and immunomodulant effects and may be useful for the treatment of hypertension, migraine, cluster headache, arthritis, regulation of appetite and in the treatment of eating disorders such as obesity, anorexia nervosa and bulimia nervosa.

There is thus provided in a further aspect of the invention a compound of formula (I) for use in therapy, in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of formula (I) as an active therapeutic substance.

There is also provided as another aspect of the invention a compound of formula (I) for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of the melatonin system.

In an alternative or further aspect of the invention there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I), in particular for the treatment of conditions associated with a disturbed functioning of the melatonin system.

It will be appreciated by those skilled in the art that reference herein to therapy and treatment extends to prophylaxis as well as the treatment of established symptoms.

While it is possible that, for use in therapy, a compound of formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

WO 95/17405

PCT/EP94/04220

5

There is further provided by the present invention a process of preparing a pharmaceutical formulation, which process comprises mixing a compound of formula (I) with one or more pharmaceutically acceptable carriers therefor.

5 Pharmaceutical formulations include those suitable for oral, rectal, vaginal, nasal, topical or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into
10 association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with
15 pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically
20 acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For topical administration in the mouth, the compositions may take the form
30 of buccal or sub-lingual tablets, drops or lozenges formulated in conventional manner.

For topical administration to the epidermis the compounds may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base

WO 95/17405

PCT/EP94/04220

6

with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending and/or colouring agents.

5 The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

10 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

15 Pessaries for vaginal administration may be formulated in a similar manner.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

20 For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

25 Any of the pharmaceutical compositions described above may be presented in a conventional manner associated with controlled release forms.

30 The active ingredient may conveniently be presented in unit dose form. A convenient unit dose formulation contains the active ingredient in an amount of from about 0.01mg to about 200mg.

35 It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular compound used and the frequency and route of administration and will ultimately be at the discretion of

the attendant physician. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

5 A proposed dose of the compounds of the invention for oral, rectal, vaginal, intranasal, topical or parenteral administration to man (of approximately 70kg bodyweight) for the treatment of conditions associated with a disturbed functioning of the melatonin system is 0.01 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

10 For oral administration a unit dose will preferably contain from 0.1 to 200mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 5 mg of the active ingredient.

15 Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 1 mg to 100 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

20 Dosages of the compounds of the invention for rectal, vaginal, intranasal or topical administration are similar to those for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents such as a hypnotic or antidepressant agent, or an anti-cancer agent such as tamoxifen, or in combination with radiation therapy to treat cancer.

25 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a compound of formula (I) together with at least one other therapeutic agent and one or more pharmaceutically acceptable carriers therefor comprise a further aspect of the invention.

30 When compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

35 When such combinations are employed the dose of each component of the combination will in general be that employed for each component when used alone.

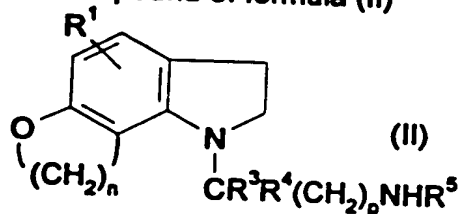
WO 95/17405

PCT/EP94/04220

8

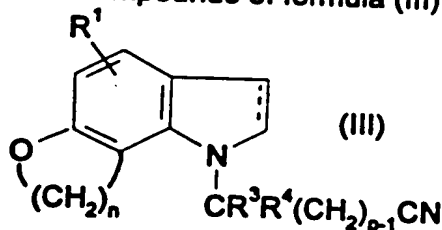
Compounds of formula (I) and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof, may be prepared by methods known in the art for the preparation of analogous compounds. In particular the compounds of formula (I) may be prepared by the methods outlined below and which form a further aspect of the invention. In the following processes, R^1 , R^3 , R^4 , R^5 , n and p are as defined for formula (I).

According to one general process (A) a compound of formula (I) may be prepared by acylation of a compound of formula (II)



Suitable acylating agents which may conveniently be used in the above process include acid anhydrides and acid halides. The reaction is conveniently effected in a suitable solvent such as an ether (e.g. diethyl ether, tetrahydrofuran or dioxan), a hydrocarbon such as toluene or a halogenated hydrocarbon (e.g. dichloromethane), preferably in the presence of a base such as pyridine or a tertiary amine (e.g. diisopropylethylamine), at a temperature in the range of 0 to 100°C, preferably 0 to 20°C.

Compounds of formula (II) in which R^5 is hydrogen may conveniently be prepared by the reduction of compounds of formula (III)



(wherein the dotted line indicates an optional double bond). The reduction may conveniently be effected using a boron hydride reducing agent such as borane-tetrahydrofuran complex in an ether solvent (e.g. tetrahydrofuran) optionally in the presence of a suitable acid (e.g. trifluoroacetic acid, hydrochloric acid or the like) at a suitable temperature, for example from 0° to 100°C. Alternatively, the reduction may employ catalytic hydrogenation in the presence of a noble metal catalyst, such as platinum, palladium or the like, in a suitable organic solvent,

WO 95/17405

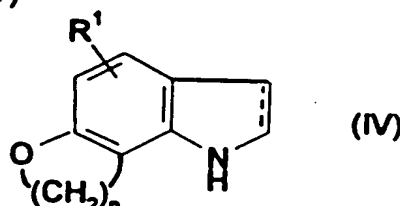
PCT/EP94/04220

9

such as an alcoholic solvent, e.g. ethanol, conveniently at a temperature in the range of 0° to 100°C, aptly at room temperature.

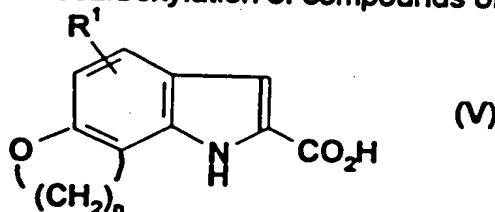
Compounds of formula (II) in which R⁵ is C₁₋₆ alkyl may be prepared by N-alkylation of compounds of formula (II) in which R⁵ is hydrogen using standard procedures.

Compounds of formula (III) may conveniently be prepared by alkylating compounds of formula (IV)



using an agent HalCR³R⁴(CH₂)_{p-1}CN in which Hal is a halogen atom (fluorine, bromine, chlorine or iodine), suitably in the presence of a base. The alkylation may be carried out under standard conditions. For example, the reaction may be effected in a ketonic solvent in the presence of an alkali or alkaline earth metal carbonate (e.g. potassium carbonate) at an elevated temperature (e.g. under reflux). Alternatively, the reaction may be effected in dimethylformamide in the presence of an alkali metal hydride (e.g. sodium hydride) at about ambient temperature.

Compounds of formula (IV) in which the dotted line indicates a double bond may be prepared by the decarboxylation of compounds of formula (V)



Thus, compounds of formula (V) may be decarboxylated by heating the compounds at a very high temperature (e.g. at about 250°C), optionally in the presence of copper and a suitable copper salt, such as copper (I) oxide, cuprous oxide and the like.

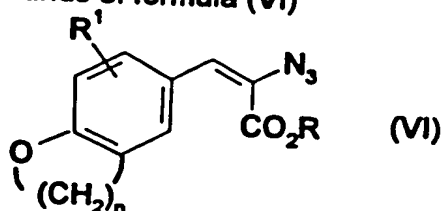
Compounds of formula (IV) in which the dotted line indicates a double bond may be converted to the corresponding saturated analogues of formula (IV) by reduction, for example using the conditions described above to prepare the compounds of formula (II) from compounds of formula (III).

WO 95/17405

PCT/EP94/04220

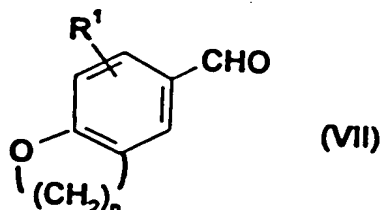
10

Compounds of formula (V) may be prepared by the cyclisation and deesterification of compounds of formula (VI)



5 (wherein R is a C₁₋₆ alkyl group, e.g. methyl). The cyclisation reaction may conveniently be effected by heating (VI) to reflux in an aromatic hydrocarbon solvent (e.g. xylene). Conversion of the so-formed ester to the corresponding acid of formula (V) involves routine hydrolysis, for example using a base such as a hydroxide (e.g. sodium hydroxide) at an elevated temperature (e.g. under reflux).

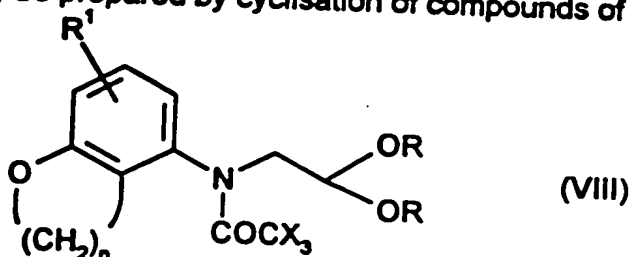
10 Compounds of formula (VI) may be prepared by treating compounds of formula (VII)



with an alkyl azidoacetate in the presence of a strong base (e.g. potassium tert-butoxide) at a temperature of from -20° to +10°C.

15 Compounds of formula (VII) are either known compounds described, for example, in WO 86/07056 or may be prepared by methods analogous to those described therein.

Alternatively compounds of formula (IV) in which the dotted line indicates a double bond may be prepared by cyclisation of compounds of formula (VIII)



20

wherein X represents a halogen atom (e.g. fluorine) and R is a C₁₋₆ alkyl group, such as methyl or ethyl. Preparation of compounds of formula (IV) typically

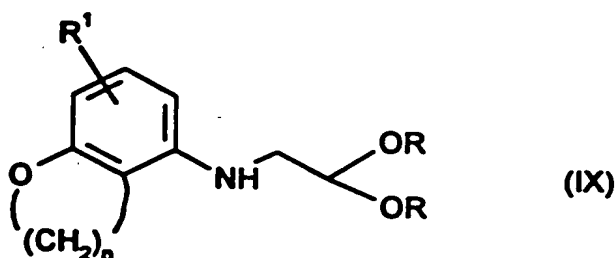
WO 95/17405

PCT/EP94/04220

11

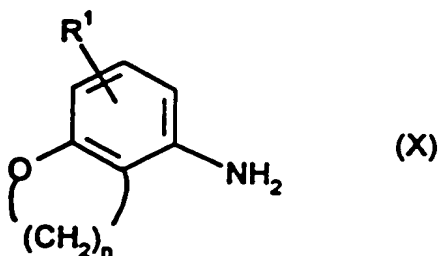
involves addition of a solution of compounds of formula (VIII) (suitably in a chlorinated organic solvent such as dichloromethane, dichloroethane or the like) to an acidic medium, such as halogenated acetic acid and/or acetic anhydride optionally in a chlorinated organic solvent as described above. Suitably the addition is carried out at 0°C under an inert atmosphere such as nitrogen. The reaction may be progressed by allowing the reagents to reach room temperature, and stirring for about 18 to 20 hours. The resulting mixture is generally treated with a base, such as an alkali metal hydroxide, prior to extraction of desired compounds of formula (IV).

Compounds of formula (VIII) are suitably prepared by acylation of compounds of formula (IX)



employing suitable acylating agents such as acid anhydrides and acid halides. Suitably a halogenated acetic anhydride (aptly trifluoroacetic anhydride) in a chlorinated organic solvent as described above is added to a solution of a compound of formula (IX) in a basic solvent, such as triethylamine and the like. Generally the addition is carried out at 0°C under an inert atmosphere such as nitrogen.

Preparation of compounds of formula (IX) suitably employs known starting materials of formula (X) shown below, which starting materials can be prepared according to J. Heterocyclic Chem., (1973), Vol 10(4), page 623. Compounds of formula (X)



25

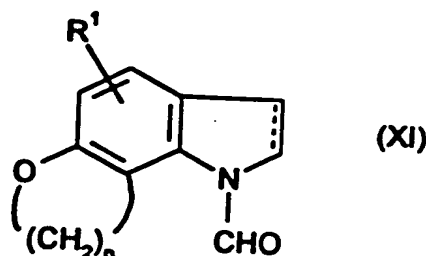
WO 95/17405

PCT/EP94/04220

12

are aptly reacted with a suitable acetal derivative, conveniently in the presence of a base (an alkali metal carbonate being an example of an appropriate base), with heating over a prolonged period of time (such as 40 to 65 hours) at an elevated temperature in the range of 90° to 110°C, in order to yield compounds of formula (IX).

Compounds of formula (I) in which R¹ represents halogen may be prepared via compounds of formulae (II), (III) and (IV) wherein R¹ represents halogen employing process steps substantially as hereinbefore described. Suitably compounds of formula (IV) in which R¹ represents halogen are prepared from compounds of formula (XI) wherein R¹ represents halogen and the dotted line indicates an optional double bond.



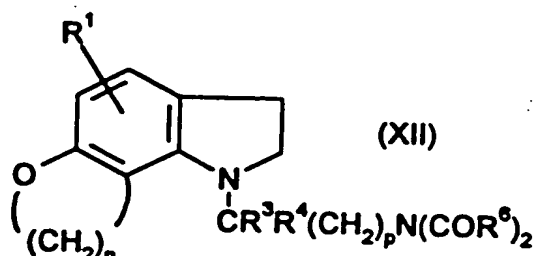
Aptly a compound of formula (XI) is dissolved in an organic solvent, such as an alcoholic solvent, acidified, and the mixture subjected to stirring and refluxing for a suitable length of time to yield a corresponding compound of formula (IV).

Conveniently a compound of formula (XI) wherein R¹ represents halogen as described above is prepared from a corresponding compound of formula (XI) wherein R¹ represents hydrogen by halogenation employing suitable halogenating agents and techniques.

Suitably compounds of formula (XI) wherein R¹ represents hydrogen as described above may be prepared from compounds of formula (IV) wherein R¹ represents hydrogen by reaction of the latter with an appropriate anhydride in an acidic medium.

According to a further embodiment of the present invention, there is provided a further general process (B) wherein a compound of formula (I) may be prepared from a compound of formula (XII)

13

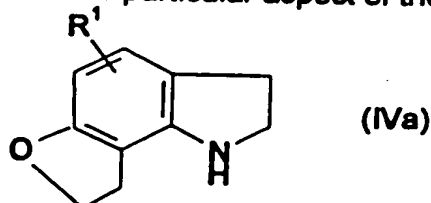


suitably by stirring for several hours (17 to 19 hours) in a basic medium, conveniently an alkali metal hydroxide or the like, under an inert atmosphere such as nitrogen, followed by refluxing for 1 to 2 hours.

5 Aply a compound of formula (XII) may be prepared by acylation of a compound of formula (II) employing acylation techniques substantially as hereinbefore described.

10 According to a yet further embodiment of the present invention, there is provided a general process (C) whereby a compound of formula (I) may be prepared by alkylating a saturated compound of formula (IV). Suitably alkylation is achieved by refluxing a compound of formula (IV) together with an alkylating agent over several days. Suitable alkylating agents include $\text{HalCR}^3\text{R}^4(\text{CH}_2)_p\text{NR}^5\text{COR}^6$ (wherein Hal, R^3 , R^4 , R^5 , R^6 and p are as hereinbefore defined), ANR^5COR^6 wherein A represents a 2-membered alkyl chain or the like.

15 Compounds of formulae (II) - (IX), (XI) and (XII) are novel intermediates and represent further individual aspects of the present invention. Compounds of formula (IVa) represent a further particular aspect of the invention.



20 According to another general process (D), a compound of formula (I) may be prepared by subjecting a protected derivative of a compound of formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, according to a further aspect of the invention, the following reactions may according to process (D), if desirable and/or if necessary, be carried out in any appropriate sequence:

25 (i) removal of any protecting groups; and

(ii) conversion of a compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt thereof.

Thus, at an earlier stage in the preparation of a compound of formula (I) it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1991).

According to another general process (E), compounds of formula (I) may be prepared from other compounds of formula (I) by interconversion reactions. In particular, acid addition salts of compounds of formula (I) may be prepared from a corresponding compound of formula (I) by suitable acid treatment, for example addition of a suitable acid, such as hydrochloric acid, generally in the presence of an organic solvent such as an alcohol or ester. Aptly the reagents may be stirred at room temperature for a convenient length of time. Alternatively, an acid may be added dropwise to a solution of a compound of formula (I) in an appropriate organic solvent as described above, optionally under an inert atmosphere such as nitrogen.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. ethanol).

Compounds of the invention may be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent.

Individual enantiomers of the compounds of the invention may be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using chiral HPLC.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the

sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples which should not be construed as constituting a limitation thereto. All temperatures are in °C.

5 THF means tetrahydrofuran. EtOH means ethanol. EtOAc means ethyl acetate. DMF means dimethylformamide. NH₃ means commercially available aqueous ammonium hydroxide. TFA means trifluoroacetic acid. TFAA means trifluoroacetic anhydride. Dried means dried over anhydrous sodium sulphate (unless otherwise stated). Chromatography was performed on silica (Merck 9385 unless otherwise stated). System A is dichloromethane/ethanol/aqueous ammonia. T.l.c. means thin layer chromatography on silica gel. The n.m.r. analysis was conducted at 250MHz.

10

Intermediate 1

15 2-Azido-3-(2,3-dihydro-benzofuran-5-yl)-acrylic acid methyl ester

To a cold (-10°C) stirred solution of potassium tert-butoxide (6.06g) in dry methanol (40ml) was added dropwise a mixture of 2,3-dihydrobenzofuran-5-carboxaldehyde (2g) and methyl azidoacetate (6.21g). The mixture was stirred for 1h at -10°C and then stored at 0°C for 18h. The resulting pale yellow microcrystals were collected by filtration to give the title compound (3.12g), m.p. 77-80°C.

20

Intermediate 2

7,8-Dihydro-1H-furo[2,3-g]indole-2-carboxylic acid

25 A solution of Intermediate 1 (3.1g) in xylene (350ml) was heated to reflux for 2h. The cooled mixture was washed with water (100ml) and then the aqueous layer extracted with xylene (50ml). The combined organic phases were dried and evaporated, and the residue dissolved in ethanol (40ml). 2N Sodium hydroxide was added (20ml) and the mixture heated to reflux for 2h. The ethanol was

30 evaporated and the mixture extracted with ether (2x50ml). The aqueous layer was then acidified and extracted with EtOAc (2x75ml). The dried extracts were evaporated to give the title compound as a yellow/orange solid (878mg), m.p. 160°C (chars) 213°C (dec.).

35 Intermediate 3

WO 95/17405

PCT/EP94/04220

16

7.8-Dihydro-1H-furo[2,3-g]indole

Intermediate 2 (875mg) was placed in a pre-heated Woods metal bath (ca. 250°C) for 2min until CO₂ evolution had ceased. The material was pre-absorbed onto silica gel and then chromatographed (35g). Elution with EtOAc:cyclohexane (1:4) gave the title compound as a beige solid (232mg).

¹H n.m.r. (CDCl₃) 7.82δ (1H, br s), 7.4δ (1H, d), 7.09δ (1H, m), 6.73δ (1H, d), 6.52δ (1H, m), 4.67δ (2H, t), 3.32δ (2H, t).

Intermediate 42.3.7.8-Tetrahydro-1H-furo[2,3-g]indole

Intermediate 3 (275mg) was dissolved in borane THF complex (1M solution, 2.6ml) and was stirred at 0°C under N₂, then trifluoroacetic acid (2.6ml) was added dropwise. Stirring was maintained at 0°C for 45min and saturated potassium carbonate solution added. The mixture was extracted with EtOAc (2x30ml). The dried extracts were evaporated and the residue chromatographed on silica gel (30g). Elution with EtOAc:cyclohexane (1:2) gave the title compound as a pale brown oil, which solidified (215mg), m.p. 48-50°C.

T.l.c. EtOAc:cyclohexane (1:2) R_f 0.25.

Intermediate 5(2.3.7.8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)acetonitrile

A mixture of Intermediate 4 (122mg), iodoacetonitrile (0.06ml) and potassium carbonate (105mg) in methyl isobutyl ketone (5ml) was heated to reflux, under N₂, for 18h. The cooled mixture was partitioned between 2N Na₂CO₃ (20ml) and EtOAc (2x30ml). The dried extracts were evaporated and the residue chromatographed on silica gel (35g). Elution with EtOAc:cyclohexane (1:3) gave the title compound as a beige solid (123mg), m.p. 122-4°C.

T.l.c. EtOAc:cyclohexane (1:2) R_f 0.37.

Intermediate 6(7.8-Dihydro-1H-furo[2,3-g]indol-1-yl)acetonitrile

To a stirred solution of Intermediate 3 (227mg) in dry DMF (8ml), was added sodium hydride (60% in oil, 85mg). The mixture was stirred for 0.5h and then chloroacetonitrile (0.13ml) was added dropwise. The mixture was then left to

stand at 20°C for 2 days and was then partitioned between 2N Na₂CO₃ solution (60ml) and EtOAc (2x70ml). The dried extracts were evaporated and the residue chromatographed on silica gel (40g). Elution with EtOAc:cyclohexane (1:3) gave the title compound as an off-white solid (109mg).

5 ¹H n.m.r. (CDCl₃) 7.38δ (1H,d), 6.9δ (1H,d), 6.77δ (1H,d), 6.53δ (1H,d), 5.04δ (2H,s), 4.70δ (2H,t), 3.65 (2H,t).

Intermediate 7

2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)ethylamine

10 (a) A solution of Intermediate 6 (160mg) in dry THF (5ml) was treated with borane THF complex (1M in THF, 8ml) and was stirred, under N₂, at 20°C for 18h. The mixture was then cooled (0°C) and trifluoroacetic acid (5ml) added. After a further 30min saturated potassium carbonate solution was added, dropwise initially, and then the mixture was extracted with EtOAc (2x40ml). The dried extracts were evaporated and chromatographed on silica gel (20g). Elution with System A (100:8:1) gave the title compound as a pale brown semi-solid (80mg).

15 ¹H n.m.r. (CDCl₃) 6.82δ (1H,d), 6.18δ (1H,d), 4.52δ (2H,t), 3.37δ (2H,t), 3.32-3.2δ (4H,2xt), 2.97-2.87δ (4H,2xt), 1.8δ (2H,br s).

20 (b) To a stirred, refluxing, solution of Intermediate 5 (203mg) in dry THF (10ml) was added dropwise borane THF complex (1M solution, 3ml). Heating was maintained for 5h and then the mixture was cooled, and methanol (3ml) added, cautiously at first. 2N HCl (3ml) was then added, and the mixture heated to reflux for a further 1h. The cooled mixture was then partitioned between saturated K₂CO₃ (40ml) and EtOAc (2x35ml). The dried extracts were evaporated and the residue chromatographed on silica gel (25g). Elution with System A (100:8:1) gave the title compound as a pale yellow oil which solidified (166mg). The n.m.r. data for this solid was consistent with that for the same compound prepared in part (a) above.

30

Intermediate 8

Chroman-5-yl-(2,2-diethoxy-ethyl)-amine

35 Bromoacetaldehyde diethyl acetal (11.8ml) was added to a mixture of chroman-5-yl-amine (5.85g) (prepared according to J. Heterocyclic Chem., (1973), Vol 10

WO 95/17405

PCT/EP94/04220

18

(4) page 623), and potassium carbonate (10.84g) in dry DMF (70ml) at room temperature under N₂. The mixture was heated at 100°C for 60h. The cooled mixture was partitioned between water (800ml) and ether (3x200ml). The combined organic extracts were washed with brine/water 1:1 (2x200ml) and dried. The solvent was evaporated and the residue purified by flash column chromatography on silica. Elution with cyclohexane/ethyl acetate 6:1 gave the title compound as a pale yellow oil (8.0g).
T.l.c. SiO₂ cyclohexane/ethyl acetate 6:1, Rf 0.35.

10 Intermediate 9

N-Chroman-5-yl-N-(2,2-diethoxy-ethyl)-2,2,2-trifluoro-acetamide

Trifluoroacetic anhydride (4.67ml) in dry dichloromethane (10ml) was added dropwise to a solution of Intermediate 8 (7.99g) and triethylamine (4.62ml) in dry dichloromethane (190ml) at 0°C under N₂. The mixture was allowed to warm to room temperature and stirred for 2h. The mixture was washed with water (2x100ml) and dried. The solvent was evaporated to give the title compound as a pale yellow oil (10.35g).
T.l.c. cyclohexane/ethyl acetate (6:1), Rf 0.6

20 Intermediate 10

1,7,8,9-Tetrahydro-pyranof[2,3-g]indole

A solution of Intermediate 9 (0.1g) in dry dichloromethane (1ml) was added dropwise to a solution of TFA (1.5ml) and TFAA (1.0ml) in dry dichloromethane (10ml) at 0°C under N₂. The mixture was allowed to warm to room temperature and stirred for 20h. The solution was cooled and basified to pH12 with 5% potassium hydroxide in methanol. The mixture was stirred for 5min, then evaporated. The residue was partitioned between water (15ml) and ethyl acetate (3x10ml). The combined organic extracts were washed with brine (1x20ml) and dried. The solvent was evaporated and the residue purified by flash chromatography on silica. Elution with cyclohexane/ethyl acetate 10:1 gave the title compound as a colourless solid (21.7mg).
T.l.c. cyclohexane/ethyl acetate (4:1), Rf 0.35.

Intermediate 11

35 1,2,3,7,8,9-Hexahydro-pyranof[2,3-g]indole

5 Borane (1.0M in THF; 5ml) was added dropwise to a solution of Intermediate 10 (434mg) in dry THF (10ml) at 0°C under N₂. Trifluoroacetic acid (32ml) was then added dropwise and the mixture stirred for 10min at 0°C. 2N sodium hydroxide (8ml) was added dropwise cautiously at 0°C to pH12. The mixture was then partitioned between water (15ml) and ethyl acetate (3x15ml). The combined organic extracts were washed with brine (1x20ml) and dried. The solvent was evaporated and the mixture was purified by flash column chromatography on silica. Elution with cyclohexane/ethyl acetate 4:1 gave the title compound as a colourless gum (222mg).

10 T.l.c. Ethyl acetate/cyclohexane (4:1), R_f 0.3.

Intermediate 12

(2,3,8,9-Tetrahydro-7H-pyrano[2,3-g]indol-1-yl)-acetonitrile

15 Iodoacetonitrile (0.11ml) was added to a mixture of Intermediate 11 (222mg) and potassium carbonate (210mg) in MIBK (10ml) at room temperature. The mixture was heated under reflux for 5h, cooled to room temperature, then partitioned between water (15ml) and ethyl acetate (3x15ml). The combined organic extracts were washed with brine (1x20ml) and dried (MgSO₄). The solvent was evaporated and the residue purified by flash column chromatography on silica. Elution with cyclohexane/ethyl acetate 5:1 gave the title compound as a colourless gum which crystallised on standing (0.25g).

20 T.l.c. cyclohexane/ethyl acetate (3:1), R_f 0.37.

Intermediate 13

2-(2,3,8,9-Tetrahydro-7H-pyrano[2,3-g]indol-1-yl)-ethylamine

25 Borane (1.0M; 2.27ml) was added dropwise to a solution of Intermediate 12 (243mg) in dry THF (5ml) at 0°C under N₂. The solution was heated under reflux for 3h, cooled to 0°C and methanol (1ml) was added cautiously dropwise until effervescing ceased. 2N HCl (2ml) was added (to pH1) and the mixture heated under reflux for 15min, cooled to 0°C and basified to pH12 with 2N NaOH (3ml). The mixture was partitioned between water (10ml) and ethyl acetate (3x15ml). The combined organic extracts were washed with brine (1x15ml) and dried. The solvent was evaporated and the residue purified by flash column chromatography on silica. Elution with

30

WO 95/17405

PCT/EP94/04220

20

dichloromethane/ethanol/ammonia 100:8:1 gave the title compound as a colourless gum (160mg).

T.l.c. Dichloromethane/ethanol/ammonia (100:8:1), Rf 0.3.

5 Intermediate 14

2,3,7,8-Tetrahydro-1H-furo[2,3-g]indole-1-carbaldehyde

To a stirred solution of Intermediate 4 (320mg) in formic acid (3ml) was added dropwise acetic anhydride (1ml). The mixture was then heated to ca. 60°C for 20min. The mixture was then added cautiously to 2N Na₂CO₃, and was extracted into EtOAc. Evaporation of the dried extract gave an off-white solid (360mg).

T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 400:8:1, Rf 0.29

Intermediate 15

5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indole-1-carbaldehyde

A stirred solution of Intermediate 14 (180mg) in glacial acetic acid (4ml) was treated with N-chlorosuccinimide (140mg) and was stirred for 7h. The mixture was partitioned between 2N Na₂CO₃ and EtOAc. Evaporation of the dried extracts gave a grey solid (218mg).

T.l.c. (SiO₂) EtOAc:cyclohexane; 1:1, Rf 0.19

Intermediate 16

5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indole

Intermediate 15 (210mg) was dissolved in methanol (5ml) and 2N HCl (1ml) added. The mixture was stirred at 20°C for 18h, then at reflux for 1h. The mixture was allowed to cool, and the methanol evaporated. The residue was then partitioned between 2N Na₂CO₃ and EtOAc. The dried extracts were evaporated to give a brown solid (166mg).

T.l.c. (SiO₂) EtOAc:cyclohexane; 1:1, Rf 0.36

Intermediate 17

(5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-acetonitrile

A stirred solution of Intermediate 16 (165mg), iodoacetonitrile (0.073ml) and potassium carbonate (140mg) in methyl isobutyl ketone (10ml) was heated to reflux for 18h under N₂. The mixture was cooled, and partitioned between

2N Na₂CO₃ and EtOAc. The dried extracts were evaporated to give a dark residue which was chromatographed on silica gel. Elution with CH₂Cl₂:EtOH:NH₃; 400:8:1 gave a pale brown solid (155mg). T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 400:8:1, R_f 0.67

5

Intermediate 182-(5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethylamine

A mixture of Intermediate 17 (150mg) in dry THF (5ml) containing borane THF (1M in THF, 1.9ml) was heated to reflux, under N₂, for 18h. The mixture was cooled, and methanol (2ml) added dropwise. 2N HCl (4ml) was then added, and the mixture heated to reflux for a further 1h. After cooling, the mixture was partitioned between saturated K₂CO₃ and EtOAc. The dried extracts were evaporated, and the red crystalline solid chromatographed on silica gel. Elution with CH₂Cl₂:EtOH:NH₃; 100:8:1 gave a pink crystalline solid (110mg).

10

15

T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 100:8:1, R_f 0.44

Intermediate 19Cyclopropanecarboxylic acid (cyclopropanecarbonyl)-[2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-amide

To a cold (0°C) stirred solution of Intermediate 7 (111mg) in CH₂Cl₂ (10ml) and diisopropylethylamine (0.14ml) was added cyclopropyl carbonyl chloride (0.074ml) dropwise under N₂. The cooling bath was removed and the mixture stirred at 20°C for 18h. The mixture was partitioned between 2N Na₂CO₃ and EtOAc. The dried extracts were evaporated and the residue chromatographed on silica gel. Elution with EtOAc:cyclohexane; 1:4 gave a colourless oil (141mg) which slowly crystallised.

20

25

T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 200:8:1, R_f 0.86

Intermediate 20(2,2-Diethoxy-ethyl)-(2,3-dihydro-benzofuran-4-yl)-amine

A mixture of 2,3-dihydro-benzofuran-4-ylamine (preparation. J. Heterocyclic Chem., 18, 1333 (1980)) (4.34g), potassium carbonate (8.87g) and bromoacetaldehyde diethyl acetal (9.7ml) in dry DMF (60ml) was heated to 100°C for 2 days under . The mixture was cooled and was partitioned between water and ethyl acetate. The dried extracts were evaporated and the residue

30

35

WO 95/17405

PCT/EP94/04220

22

chromatographed on silica gel (250g). Elution with ethyl acetate:cyclohexane 1:4 gave the title compound as a pale yellow oil (4.95g).

T.l.c. EtOAc:cyclohexane 1:1, Rf 0.73.

Analysis Found: C, 66.8; H, 8.5; N, 5.35;

5 $C_{14}H_{21}NO_3$ requires: C, 66.9; H, 8.4; N, 5.55%

Intermediate 21

N-(2,2-Diethoxy-ethyl)-N-(2,3-dihydro-benzofuran-4-yl)-2,2,2-trifluoro-acetamide

10 Trifluoroacetic anhydride (4.12ml) was added dropwise to a cooled (0°C) stirring solution of the intermediate 20 (6.67g) and triethylamine (4.06ml) in dichloromethane (100ml) under nitrogen. The mixture was warmed to room temperature and stirred for 1½h. The reaction mixture was partitioned between water and dichloromethane. The aqueous phase was re-extracted with dichloromethane. The combined organic layers were dried, evaporated and chromatographed on silica gel eluting with ethyl acetate:cyclohexane 1:9 gave the title compound (8.31g) as a yellow oil.

15 T.l.c. Cyclohexane:EtOAc (4:1), Rf 0.38.

Analysis Found: C, 55.30; H, 5.74; N, 3.96;

20 $C_{16}H_{20}F_3NO_4$ requires: C, 55.33; H, 5.8; N, 4.03%

Intermediate 22

7,8-Dihydro-1H-furo[2,3-g]indole

25 A solution of the intermediate 21 (8.27g) in dichloromethane (80ml) was added dropwise to a stirred solution of trifluoroacetic acid (80ml) and trifluoroacetic anhydride (53ml) in dichloromethane (800ml) at 0°C under nitrogen. This was warmed to room temperature and stirred for 20h. The cooled reaction mixture was basified with 2N sodium hydroxide and then stirred for 1½h at room temperature. The organic phase was separated and the aqueous layer was re-extracted with dichloromethane. The combined organic phases were dried, evaporated and chromatographed on silica gel eluting with EtOAc:Cyclohexane (1:9) gave the title compound as a beige solid (2.6g).

30 T.l.c. cyclohexane:ethyl acetate 7:3, Rf 0.43.

Analysis Found: C, 75.31; H, 5.65; N, 8.62;

35 $C_{10}H_9NO$ requires: C, 75.45; H, 5.70; N, 8.80%

WO 95/17405

PCT/EP94/04220

23

Example 1N-(2-(2,3,8,9-Tetrahydro-7H-pyranol[2,3-g]indol-1-yl)-ethyl)-acetamide

Acetic anhydride (0.104ml) was added to a solution of the Intermediate 13 (160mg) and pyridine (0.12ml) in dry THF (4ml) at 0°C under N₂. The mixture was allowed to warm to room temperature and stirred for 3h. The solvent was evaporated and the residue purified by flash column chromatography on silica. Elution with ethyl acetate gave the title compound as colourless crystals (151mg), m.p. 91-93°C.

T.l.c. Ethyl acetate, R_f 0.2.

Example 2N-(2-(2,3,8,9-Tetrahydro-7H-pyranol[2,3-g]indol-1-yl)-ethyl)-acetamide hydrochloride

Ethereal HCl (0.25ml) was added dropwise to a solution of the title compound of Example 1 (56mg) in ethanol (2ml) at 0°C under N₂. The solvent was evaporated and the residue triturated under ether (2x1ml). The solvent was decanted to give the title compound as a colourless solid (63mg), m.p. 179-181°C.

Analysis Found: C, 58.6; H, 7.5; N, 8.95;

C₁₅H₂₀N₂O₂.HCl requires: C, 58.6; H, 7.3; N, 9.1%

¹H N.m.r. (CD₃OD; δ) 7.2δ (1H, d), 6.9δ (1H, d), 4.24δ (2H, t), 4.07δ (2H, t), 3.6δ (4H, AA'BB'), 3.28δ (2H, t), 2.88δ (2H, t), 2.1-1.95δ (5H, m+s)

Example 3N-(2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl)-acetamide

To a stirred solution of Intermediate 7 (77mg) in dry THF (5ml) containing pyridine (0.09ml) was added acetic anhydride (0.06ml). After 18h at 20°C the mixture was partitioned between 2N Na₂CO₃ (30ml) and EtOAc (2x30ml). The dried extracts were evaporated and the residue chromatographed on silica gel (20g). Elution with System A (200:8:1) gave the title compound as a colourless crystalline solid (56mg), m.p. 126-7°C.

T.l.c. System A (100:8:1) R_f 0.42.

Example 4

N-[2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide hydrochloride

The title compound of Example 3 (334mg) was dissolved in ethyl acetate (20ml) and was treated with ethereal HCl (1.35ml). This was stirred at room temperature for 2h and then the solvent was evaporated to give the title compound as a pale green powder (383mg), m.p. 152-154°C.

T.l.c. System A 100:8:1, Rf 0.41.

Analysis Found: C, 59.45; H, 7.15; N, 9.55; Cl, 12.8;

C₁₄H₁₈N₂O₂.HCl requires: C, 59.45; H, 6.75; N, 9.9; Cl, 12.55%

Example 5N-[2-(5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide

A solution of Intermediate 18 (107mg) in dry THF (5ml) and dry pyridine (0.11ml) was treated with acetic anhydride (0.085ml) and left for 2 days at 20°C under N₂. The mixture was partitioned between 2N Na₂CO₃ and EtOAc. The dried extracts were evaporated, and the residue chromatographed on silica gel. Elution with CH₂Cl₂:EtOH:NH₃; 200:8:1 gave the title compound as a colourless crystalline solid (114mg), m.p. 147-9°C.

Assay Found: C, 60.15; H, 6.35; N, 10.05;

C₁₄H₁₇ClN₂O₂ requires: C, 59.9; H, 6.1; N, 10.0%

T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 100:8:1, Rf 0.69

Example 6Cyclopropanecarboxylic acid [2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-amide

Intermediate 19 (140mg) was stirred in methanol (10ml) and 2N NaOH (4ml) at 20°C under N₂ for 18h, and then at reflux for 1h. The mixture was diluted with water and extracted with EtOAc. The dried extracts were evaporated giving the title compound as a colourless solid (111mg), m.p. 147-9°C.

Assay Found: C, 70.9; H, 7.45; N, 10.15;

C₁₆H₂₀N₂O₂ requires: C, 70.55; H, 7.4; N, 10.3%

T.l.c. (SiO₂) CH₂Cl₂:EtOH:NH₃; 200:8:1, Rf 0.48

Example 7N-[2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide

WO 95/17405

PCT/EP94/04220

25

5 A mixture of Intermediate 4 (50mg), potassium iodide (1g) and N-(2-chloroethyl)acetamide (96mg) in acetone (5ml) was heated to reflux for 2 days. The cooled mixture was partitioned between water and ethyl acetate. The extracts were dried, and evaporated, and the residue chromatographed on silica gel. Elution with $\text{CH}_2\text{Cl}_2:\text{EtOH}:\text{NH}_3$; 400:8:1 gave a sample of desired material (69mg).

T.l.c. (SiO_2) System A; 100:8:1, Rf 0.42

^1H n.m.r. agrees with assignment for alternative routes of preparation.

10 6.856 (1H,d), 6.26 (1H,d), 5.866 (1H,brs), 4.526 (2H,t), 3.5-3.36 (6H,m), 3.226 (2H,t), 2.936 (2H,t), 2.06 (3H,s)

Example 8

15 Compounds of formula (I) have been shown to exhibit high affinity and selectivity for binding to melatonin receptors in chicken retinal membranes, measured according to the methods of Dubocovich and Takahashi (Proc. Natl. Acad. Sci. (1988), 84, 3916-3820). The compounds of formula (I) have either melatonin agonist or antagonist activity as demonstrated in rabbit retina, according to the methods of Dubocovich (J. Pharmacol. Exp. Therap. (1985), 234, 395-401). The results obtained for particular compounds according to the present invention are as follows:

Compound	Chicken retina K_i (nM)	Rabbit retina IC_{50} (nM)
Example 2	4.92	0.950
25 Example 3	0.42	0.040
Example 5	3.21	0.004
Example 6	1.68	0.200

Example 9

30 Compounds of formula (I) have been included in pharmacy formulations, and details of such formulations are given below.

WO 95/17405

PCT/EP94/04220

26

TABLETS FOR ORAL ADMINISTRATION**A. Direct Compression**

	mg/tablet
Active ingredient	49.0
Anhydrous Lactose	55.2
Microcrystalline cellulose	37.5
Pregelatinised maize starch	7.5
Magnesium stearate	0.8

5 The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets using a tablet machine fitted with appropriately sized concave punches.

B. Wet Granulation

	mg/tablet
Active ingredient	7.0
Lactose BP	146.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression weight	200.0

10

15 The active ingredient was sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets using suitable diameter punches.

Tablets of other strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

WO 95/17405

PCT/EP94/04220

27

	Unit formula (mg/tablet)
Active ingredient/lactose granule*	93.0
Microcrystalline cellulose Ph Eur	5.5
Croscarmellose Sodium USNF	1.0
Magnesium Stearate Ph Eur	0.5

* Active ingredient/lactose granule	mg
Active ingredient	140.0
Lactose Ph Eur 170 mesh	140.0
Purified water Ph Eur	qs +

5

+ The water does not appear in the final product. Typical range 100-140g per kg of blend.

10

The active ingredient and lactose were mixed together and granulated by the addition of purified water. The granules obtained after mixing were dried and passed through a screen, and the resulting granules were then mixed with the other tablet core excipients. The mix is compressed into tablets.

15

The tablets may be film coated with suitable film-forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated, or enteric coated.

Coating Suspension	% w/w
Hydroxypropyl methylcellulose Ph Eur	10.0
Opaspray white #	5.0
Purified water Ph Eur to	100.0++

WO 95/17405

PCT/EP94/04220

28

++ The water does not appear in the final product. The maximum theoretical weight of solids applied during coating is 11mg/tablet.

5 # Opaspray white is a proprietary film coating suspension, obtainable from Colorcon Ltd, UK, which contains hydroxypropyl methylcellulose and titanium dioxide.

10 The tablets were film coated using the coating suspension in conventional film coating equipment.

EFFERVESCENT TABLET

	mg/tablet
Active ingredient	140.0mg
Sodium bicarbonate	656.4mg
Monosodium citrate anhydrous	659.5mg
Aspartame	40.0mg
Polyvinylpyrrolidone	32.0mg
Sodium benzoate	48.0mg
Orange flavour	16.0mg
Lemon flavour	8.0mg
Absolute alcohol for granulation	

15 The active ingredient, anhydrous monosodium citrate, sodium bicarbonate and aspartame were mixed together and granulated by the addition of a solution of the polyvinylpyrrolidone in the alcohol. The granules obtained after mixing were dried and passed through a screen, and the resulting granules were then mixed with the sodium benzoate and flavourings. The granulated material was compressed into tablets using a machine fitted with 20mm punches.

20 A rotary machine fitted with 20mm punches may also be used for tableting.

LIQUID AND CAPSULE FORMULATIONS FOR ORAL ADMINISTRATION

Liquid formulations were prepared by slow addition of active ingredient into the other ingredients at 35-50°C with constant mixing (amounts are given as percentage w/w).

5

Example	A	B
Active ingredient	18.2	18.2
Oleic acid	60.985	68.485
Polyethylene glycol 600	7.3	7.3
Propylene glycol	6.0	6.0
Polysorbate 80	7.5	-
Ascorbyl palmitate	0.015	0.015

The liquid formulations were filled into hard gelatin capsules, each capsule containing 25mg of active ingredient.

10 **CAPSULES**

	mg/capsule
Active ingredient	49.0
* Starch 1500	150.0
Magnesium Stearate BP	1.0
Fill weight	200.0

* A form of directly compressible starch.

15 The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

WO 95/17405

PCT/EP94/04220

30

SYRUP

Sucrose Free Presentation	mg/5ml dose
Active ingredient	49.0
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer)	as required
Flavour)	
Colour)	
Preservative)	
Sweetener)	
Purified water BP to	5.0ml

5

The hydroxypropylmethylcellulose was dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution was adjusted to volume and mixed. The syrup was clarified by filtration.

SUSPENSION

10

	mg/5ml dose
Active ingredient	49.0
Aluminium monostearate	75.0
Sweetening agent)	as required
Flavour)	
Colour)	
Fractionated coconut oil to	5.0ml

The aluminium monostearate was dispersed in about 90% of the fractionated coconut oil. The resulting suspension was heated to 115°C while stirring and then cooled. The sweetening agent, flavour and colour were added and the

31

active ingredient was suitably dispersed. The suspension was made up to volume with the remaining fractionated coconut oil and mixed.

SUB-LINGUAL TABLET

	(mg/tablet)
Active ingredient/lactose granule*	49.0
Compressible sugar NF	50.5
Magnesium Stearate BP	0.5
Compression Weight	100.0

The active ingredient was sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

SUPPOSITORY FOR RECTAL ADMINISTRATION

Active ingredient	49.0mg
*Witepsol W32	1.0g

* A proprietary grade of Adeps Solidus Ph Eur

A suspension of the active ingredient in molten Witepsol was prepared and filled using suitable machinery, into 1g size suppository moulds.

INJECTION FOR SUBCUTANEOUS ADMINISTRATION

	mg/ml
Active ingredient	0.896
Sodium Chloride Intravenous Infusion, BP, 0.9% w/v	to 1 ml
Batch size	2500ml

5 The active ingredient was dissolved in a portion of the Sodium Chloride
Intravenous Infusion, the solution made to volume with the Sodium Chloride
Intravenous Infusion, and the solution thoroughly mixed. The solution was filled
into clear, Type 1, glass 1ml ampoules and sealed by fusion of the glass under
a nitrogen or air headspace. The ampoules were sterilised by autoclaving at
10 121°C for not less than 15 minutes. Alternatively the solution may be sterilised
by filtration prior to filling aseptically into ampoules.

FOR INHALATION**Inhalation Cartridges**

	mg/cartridge
Active ingredient (micronised)	0.56
Lactose BP	25.00

15 The active ingredient was micronised in a fluid energy mill to a fine particle size
range prior to blending with normal tableting grade lactose in a high energy
mixer. The powder blend was filled into No 3 hard gelatin capsules on a
suitable encapsulating machine. The contents of the cartridges were
20 administered using a powder inhaler such as the Glaxo Rotahaler.

WO 95/17405

PCT/EP94/04220

33

Metered Dose Pressurised Aerosol

Suspension Aerosol	mg/metered dose	Per can
Active ingredient (micronised)	0.280	73.92mg
Oleic Acid BP	0.020	5.28mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

5 The active ingredient was micronised in a fluid energy mill to a fine particle size range. The oleic acid was mixed with the trichloromethane at a temperature of 10-15°C and the micronised drug was mixed into the solution with a high shear mixer. The suspension was metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension, were crimped onto the cans and the dichlorodifluoromethane was pressure filled into the cans through the valves.

NASAL SPRAY

	% w/v
Active ingredient	7.0
Sodium Chloride BP	0.9
Purified Water BP to	100
Shot Weight	100mg (equivalent to 7mg active ingredient)

15 The active ingredient and sodium chloride were dissolved in a portion of the water, the solution made to volume with the water and the solution thoroughly mixed.

20 The pH may be adjusted to facilitate solution of the active ingredient, using acid or alkali and/or subsequently adjusted ideally to near neutrality taking into account the pH for optimum stability. Alternatively, suitable buffer salts may be

WO 95/17405

PCT/EP94/04220

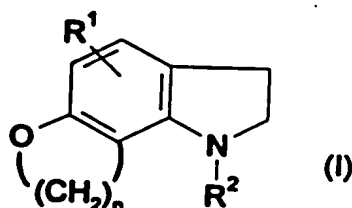
34

used. The solution may be preserved with, for example, benzalkonium chloride and phenylethyl alcohol, for a multi-dose nasal spray.

35

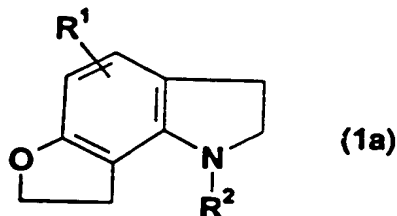
CLAIMS

1. A compound of formula (I)



wherein R¹ is hydrogen, halogen or C₁₋₆ alkyl;
 R² is a group of formula -CR³R⁴(CH₂)_pNR⁵COR⁶;
 R³, R⁴ and R⁵, which may be the same or different, are hydrogen or C₁-
 galkyl;
 R⁶ is C₁-galkyl or C₃₋₇ cycloalkyl;
 n is an integer of 2,3 or 4;
 p is an integer of 1,2,3 or 4;
 and pharmaceutically acceptable salts and solvates thereof.

2. A compound of formula (Ia)



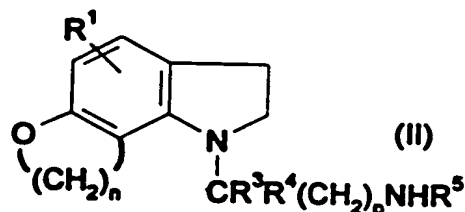
wherein R¹ is hydrogen, halogen or C₁₋₈ alkyl;
 R² is a group of formula -CR³R⁴(CH₂)_pNR⁵COR⁶;
 R³, R⁴ and R⁵, which may be the same or different, are hydrogen or C₁-
 galkyl;
 R⁶ is C₁-galkyl or C₃₋₇ cycloalkyl;
 p is an integer of 1,2,3 or 4;
 and pharmaceutically acceptable salts and solvates thereof.

3. A compound according to Claim 1 or 2, wherein R^2 represents a group $-CR^3R^4(CH_2)_pNHCOR^6$ wherein R^3 and R^4 each independently represent hydrogen or C_{1-3} alkyl, p is an integer of 1 or 2, and R^6 is C_{1-3} alkyl or C_{3-5} cycloalkyl.
- 5
4. A compound according to any of claims 1 to 3, wherein R^1 is selected from the group consisting of hydrogen, chlorine and C_{1-3} alkyl.
- 10
5. N-[2-(2,3,8,9-Tetrahydro-7H-pyrano[2,3-g]indol-1-yl)-ethyl]-acetamide;
N-[2-(5-Chloro-2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide;
Cyclopropanecarboxylic acid [2-(2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-amide;
and pharmaceutically acceptable salts and solvates thereof.
- 15
6. N-[2-(2,3,7,8-Tetrahydro-1H-furo[2,3-g]indol-1-yl)-ethyl]-acetamide and pharmaceutically acceptable salts and solvates thereof.
- 20
7. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 6, together with one or more pharmaceutically acceptable carriers therefor.
- 25
8. A process of preparing a pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 6, together with one or more pharmaceutically acceptable carriers therefor, which process comprises mixing said compound of formula (I) together with said one or more pharmaceutically acceptable carriers therefor.
- 30
9. A compound of formula (I) according to any of Claims 1 to 6, for use in therapy.
- 35
10. A compound of formula (I) according to any of Claims 1 to 6, for use in the preparation of a medicament for use in the treatment of conditions associated with a disturbed functioning of the melatonin system.

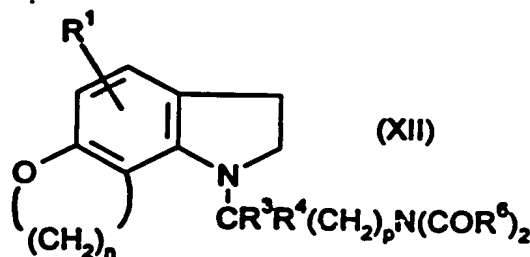
11. A method of treating a mammal, including man, comprising administration of an effective amount of a compound of formula (I) according to any of Claims 1 to 6, for the treatment of conditions associated with a disturbed functioning of the melatonin system.

12. A process of preparing a compound of formula (I) according to any of Claims 1 to 6, which process comprises:

(a) acylation of a compound of formula (II)

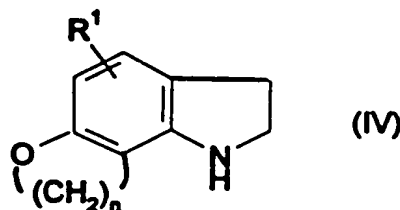


or (b) treating a compound of formula (XII)



with an alkali metal hydroxide;

or (c) alkylation of a compound of formula (IV)



WO 95/17405

PCT/EP94/04220

38

13. Compounds of formulae (II), (III), (IV), (IVa), (V), (VI), (VII), (VIII), (IX), (XI) and (XII).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/04220

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D491/048 C07D307/79 C07D311/58 C07D491/052 A61K31/40
//(C07D491/052,311:00,209:00),(C07D491/048,307:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 043 752 (SOCIETE DE RECHERCHES INDUSTRIELLES) 13 January 1982 see page 17; claims 1,17	1,7,10
X	see page 26 - page 27; claims 1,18	13
A	CANADIAN JOURNAL OF CHEMISTRY., vol.60, no.16, 1982, OTTAWA CA pages 2093 - 2098 P. T. KIM ET AL 'Synthèse de pyranno(f et g)indoles'	1
X	see page 2093 - page 2095 see page 2093 - page 2095	13
X	EP,A,0 207 605 (PFIZER) 7 January 1987 cited in the application see page 18; example 5	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"!" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 March 1995

Date of mailing of the international search report

29. 03. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340 2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

PCT/EP 94/04220

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 13 has been searched even though it relies on figures of the description. (Rule 6.2(a), PCT)
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/04220

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0043752	13-01-82	FR-A- 2485539	31-12-81
		AT-T- 7917	15-06-84
		JP-A- 57038782	03-03-82
		US-A- 4436915	13-03-84
		US-A- 4680411	14-07-87

EP-A-0207605	07-01-87	WO-A- 8607056	04-12-86
		CA-A- 1279320	22-01-91
		IE-B- 58674	03-11-93
		US-A- 4703052	27-10-87
		US-A- 4738972	19-04-88

THIS PAGE BLANK (USPTO)

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS
- ☒ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- BLURRED OR ILLEGIBLE TEXT OR DRAWING
- SKEWED/SLANTED IMAGES
- COLOR OR BLACK AND WHITE PHOTOGRAPHS
- GRAY SCALE DOCUMENTS
- LINES OR MARKS ON ORIGINAL DOCUMENT
- REFERENCE (S) OR EXHIBIT (S) SUBMITTED ARE POOR QUALITY
- OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image problem Mailbox.

THIS PAGE BLANK (USPTO)